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PATENT
Attorney Docket No.: 018484-002121US
Pitt-04/03

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Christopher H. Evans, et al.

Continuation of Application
No.: 09/096,572

Filed: June 12, 1998

For: SYSTEMIC GENE TREATMENT
OF CONNECTIVE TISSUE DISEASES

Examiner: Wilson, Michael C.

Art Unit: 1633

PRELIMINARY AMENDMENT

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-referenced application, please enter the following amendments and remarks.

IN THE SPECIFICATION:

Please delete the Table of Contents found at the beginning of the application if it has not already been deleted.

Please add the following paragraph to the specification:

Page 1, please insert the following paragraph at line 1:

This application is a continuation of U.S.S.N. 09/096,572, filed February 26, 2000, which is a continued prosecution application of U.S.S.N. 09/096,572, filed June 12, 1998, which is a divisional of U.S.S.N. 08/697,180, filed August 20, 1996 and is now U.S. Patent No. 5,766,585, which is a continuation of U.S.S.N. 08/167,642,

filed December 14, 1993, now abandoned. Each of these applications is incorporated by reference in their entirety and for all purposes.

On page 7, second paragraph , continuing to top of page 8, please delete paragraph and insert therefor:

Reactive oxygen intermediates (ROI's) formed in response to inflammatory signals have been implicated in the destruction of extracellular matrix components such as hyaluronic acid and the proteoglycans collagen and elastin. The collagens are composed of a family of fibrous proteins which are secreted by connective tissue cells. Collagen is the major protein of the extracellular matrix. Elastin, also an extracellular matrix protein expressed in connective tissue cells, forms a cross-linked network possessing both elasticity and tensile strength. Skaleric, et al. (1991, J. Immunol. 147:2559-2564) suggests that interaction of potential ROI inhibitors such as superoxide dismutase during an inflammatory episode may reduce the erosive effects of ROI's in connective tissue disorders.

On page 12, please replace paragraph three with the following new paragraph:

A nucleic acid sequence encoding an antiadhesion molecule so as to inhibit cell-cell or cell-matrix interactions prominent in the early stages of an inflammatory response may be used to practice the present invention. Therapeutic or prophylactic inhibitors of cell-cell or cell-matrix interactions include, but are not limited to, soluble ICAM-1, soluble CD44, soluble CD18 or biologically active fragments of soluble ICAM-1, soluble CD44 or soluble CD18.

On page 20, delete second paragraph, beginning on line 18 and continuing to page 21, line 19, and insert therefor:

In additional embodiments of the invention, treatment of other autoimmune disease which affect connective tissue, including but are not limited to Sjörgen's syndrome, polymyositis-dermatomyositis, systemic sclerosis (scleroderma), vasculitis syndromes, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease. Additional non-immune diseases or disorders

pathologically related to the connective tissue which are disclosed for treatment in the present invention include, but are not limited to, osteoporosis, osteogenesis imperfecta, and Paget's disease. Treatment of these diseases involves the prolonged, systemic delivery of therapeutic or prophylactic expression products encoded by nucleic acid sequences which include but are not solely limited to (1) IRAP or a biologically active fragment thereof; (2) a soluble receptor of IL-1 or a biologically active fragment thereof; (3) IL-4 or a biologically active fragment thereof; (5) a soluble receptor of TNF-α or a biologically active fragment thereof; (6) a nucleic acid sequence encoding an inhibitor of metalloproteinases or a biologically active fragment thereof, such as TIMP; (7) a nucleic acid sequence encoding an antiadhesion molecule such as soluble ICAM-1 and soluble CD-44, or biologically active fragments of soluble ICAM-1 or soluble CD-44; (8) a nucleic acid sequence encoding an anti-oxidant, such as superoxide dismutase, or a biologically active fragment thereof, and an inhibitor of nitric oxide synthase, or biologically active fragments thereof; (9) a nucleic acid sequence encoding IGF-1 or a biologically active fragment thereof, and TGF-β or a biologically active fragment thereof; (10) a nucleic acid fragment encoding constituents of the extracellular matrix, such as collagen; and (11) a soluble receptor of IL-6 or a biologically active fragment thereof. Any of the strategies disclosed within the specification may be utilized for the systemic delivery of these DNA sequences to a mammalian host in treating the hereinbefore mentioned diseases.

On page 24, please delete fourth paragraph and insert therefor:

As used herein, the term "biologically active fragment" refers to any portion or derivative of the corresponding wild-type molecule exhibiting biological activity by promoting therapeutic relief or prophylactic resistance from proteins, peptides or chemical compounds which induce inflammatory or erosive responses during pathogenesis of a connective tissue disease or disorder.

On page 25, please delete the second paragraph and insert therefor:

Figure 2 shows the cloned IRAP cDNA sequence (SEQ ID NOS:3 and 4) utilized in construction of MFG-IRAP, namely a HindIII fragment comprising the entire

coding region of human IRAP, as described in detail in Example Section 6.1.1.; SEQ ID NO:3 is the nucleotide sequence and SEQ ID:4 is the amino acid sequence for human IRAP.

On page 27, please delete third paragraph and insert therefor:

A nucleic acid sequence encoding an antiadhesion molecule so as to inhibit cell-cell or cell-matrix interactions prominent in the early stages of an inflammatory response may be used to practice the present invention. Therapeutic or prophylactic inhibitors of cell-cell or cell-matrix interactions includes, but is not limited to, soluble ICAM-1, soluble CD44 or soluble CD18.

On page 37, please delete the second paragraph and insert therefor:

In a further embodiment regarding the IRAP induced systemic treatment of rheumatoid arthritis, the DNA sequence encoding IRAP or a portion thereof is subcloned into a MoMLV retroviral vector prior to systemic delivery to the patient. Specifically, a recombinant MoMLV-IRAP construction that may be utilized in the treatment of SLE is MFG-IRAP (Figure 1), wherein the DNA sequence encoding IRAP or a portion thereof is SEQ ID NO:3 (Figure 2).

IN THE CLAIMS:

Please add claims 143-157 as follows:

143. A method of inhibiting an IL-1-induced biological response in a mammal, the method comprising administering to said mammal a polynucleotide encoding a cytokine which inhibits an IL-1-induced biological response, thereby systemically delivering the cytokine and inhibiting the IL-1 induced biological response.

144. The method of claim 143, wherein said cytokine is IRAP, or a biologically active fragment thereof.

145. The method of claim 143, wherein said cytokine is IL-10, or a biologically active fragment thereof.

146. The method of claim 143, wherein said cytokine is IL-4, or a biologically active fragment thereof.

147. The method of claim 143, wherein administration of said polynucleotide is by a viral vector.

148. The method of claim 147, wherein said viral vector comprises a retroviral or an adenoviral vector.

149. The method of claim 143, wherein said polynucleotide is introduced into a cell ex vivo and said cell is subsequently administered into said mammal.

150. The method of claim 149, wherein said cell is selected from the group consisting of bone marrow cell, peripheral blood leukocyte, and myoblast.

151. The method of claim 149, wherein said cell is autologous.

152. The method of claim 143, wherein said polynucleotide is systemically administered to said mammal by injection into the circulatory system of said mammal.

153. The method of claim 143, wherein said polynucleotide is locally administered to said mammal.

154. The method of claim 153, wherein said polynucleotide is locally administered by direct injection into a skeletal muscle of said mammal.

155. The method of claim 150, wherein said peripheral blood leukocyte is a peripheral blood lymphocyte.

156. The method of claim 143, wherein said IL-1-induced biological response is inhibited in a joint of said mammal.

157. The method of claim 143, wherein said IL-1-induced biological response comprises an increase in serum IL-6 levels.

REMARKS

The specification is amended to clearly recite the priority of the current application. No new matter is added by this amendment. Numerous paragraphs are amended herein to correct clear grammatical or typographical errors. No new matter is added by these amendments. The description of Figure 2 on page 25 is amended to recite that SEQ ID NO: 3 is the IRAP cDNA sequence and SEQ ID NO:4 is the IRAP amino acid sequence. Support for this addition may be found in SEQ ID NOs: 3 and 4 as originally filed.

Claims 1-142 are pending, and claims 143-157 are added herein. Support for the new claims are replete throughout the specification as filed. Support for new claim 143 may be found, *e.g.*, at page 11, lines 3-17, and at page 55, lines 13-15. Support for new claim 144 may be found, *e.g.*, at page 11, lines 15-16. Support for new claim 145 may be found, *e.g.*, at page 11, lines 16-17. Support for new claim 146 may be found, *e.g.*, at page 11, line 16. Support for new claim 147 may be found, *e.g.*, at page 13, lines 9-10. Support for new claim 148 may be found, *e.g.*, at page 13, lines 12-13. Support for new claim 149 may be found, *e.g.*, at page 14, lines 14-16. Support for new claim 150 may be found, *e.g.*, at page 14, lines 18-23. Support for new claim 151 may be found, *e.g.*, at page 31, lines 13-14 and at page 32, lines 1-4 and lines 8-11. Support for new claim 152 may be found, *e.g.*, at page 17, lines 1-3 and at page 54, lines 12-14. Support for new claim 153 may be found, *e.g.*, at page 13, lines 19-21 and original claim 3. Support for new claim 154 may be found, *e.g.*, at page 13, lines 19-21. Support for new claim 155 may be found, *e.g.*, at page 14, line 22. Support for new claim 156 may

be found, *e.g.*, at page 2, lines 12-20. Support for new claim 157 may be found, *e.g.*, at page 4, lines 9-10. No new matter is added by these claims.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Peter Seperack
Reg. No. 47,932

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SF 1320162 v1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

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Page 1, please insert the following paragraph at line 1:

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On page 7, second paragraph , continuing to top of page 8, a period has been inserted at the end of the paragraph. Please delete second paragraph on page 7, continuing to page 8 and insert therefor:

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On page 12, line 12, delete the phrase "includes, but is" and insert therefor --include, but are--. Please replace paragraph three with the following new paragraph:

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On page 27, line 16, third paragraph, "in" has been deleted.

--A nucleic acid sequence encoding an antiadhesion molecule so as to inhibit cell-cell or cell-matrix interactions prominent in the early stages of an inflammatory response may be used to practice the present invention. Therapeutic or prophylactic inhibitors of cell-cell or cell-matrix interactions includes, but is ~~in~~not limited to, soluble ICAM-1, soluble CD44 or soluble CD18.--

On page 37, line 8, second paragraph, "SES" has been deleted and --SEQ- - inserted therefor.

--In a further embodiment regarding the IRAP induced systemic treatment of rheumatoid arthritis, the DNA sequence encoding IRAP or a portion thereof is subcloned into a MoMLV retroviral vector prior to systemic delivery to the patient. Specifically, a recombinant MoMLV-IRAP construction that may be utilized in the

treatment of SLE is MFG-IRAP (Figure 1), wherein the DNA sequence encoding IRAP or a portion thereof is ~~SES~~ SEQ ID NO:3 (Figure 2).--

IN THE CLAIMS:

Please add claims 143-157 as follows:

--143. (New) A method of inhibiting an IL-1-induced biological response in a mammal, the method comprising administering to said mammal a polynucleotide encoding a cytokine which inhibits an IL-1-induced biological response, thereby systemically delivering the cytokine and inhibiting the IL-1 induced biological response.

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145. (New) The method of claim 143, wherein said cytokine is IL-10, or a biologically active fragment thereof.

146. (New) The method of claim 143, wherein said cytokine is IL-4, or a biologically active fragment thereof.

147. (New) The method of claim 143, wherein administration of said polynucleotide is by a viral vector.

148. (New) The method of claim 147, wherein said viral vector comprises a retroviral or an adenoviral vector.

149. (New) The method of claim 143, wherein said polynucleotide is introduced into a cell ex vivo and said cell is subsequently administered into said mammal.

150. (New) The method of claim 149, wherein said cell is selected from the group consisting of bone marrow cell, peripheral blood leukocyte, and myoblast.

151. (New) The method of claim 149, wherein said cell is autologous.

152. (New) The method of claim 143, wherein said polynucleotide is systemically administered to said mammal by injection into the circulatory system of said mammal.

153. (New) The method of claim 143, wherein said polynucleotide is locally administered to said mammal.

154. (New) The method of claim 153, wherein said polynucleotide is locally administered by direct injection into a skeletal muscle of said mammal.

155. (New) The method of claim 150, wherein said peripheral blood leukocyte is a peripheral blood lymphocyte.

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